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FILE 'REGISTRY' ENTERED AT 15:45:33 ON 15 MAY 2002
E AMLODIPINE/CN
L1 1 SEA AMLODIPINE/CN
E "(R)-(+)-AMLODIPINE"/CN
L2 1 SEA "(R)-(+)-AMLODIPINE"/CN
E "(L)-(-)-AMLODIPINE"/CN
E "(S)-(-)-AMLODIPINE"/CN
L3 1 SEA "(S)-(-)-AMLODIPINE"/CN
L4 3 SEA L1 OR L2 OR L3

FILE 'HCAPLUS' ENTERED AT 15:47:21 ON 15 MAY 2002
L5 10 SEA (L4 OR AMLODIPINE) AND CARRIER

L5 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:122825 HCAPLUS
DOCUMENT NUMBER: 136:172796
TITLE: Composition for transdermal and/or transmucosal administration of active compounds that ensures adequate therapeutic levels
INVENTOR(S): Carrara, Dario; Porto, Gabriel; Rodriguez, Jorge
PATENT ASSIGNEE(S): Antares Pharma IPL A.-G., Switz.
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002011768 | A1 | 20020214 | WO 2001-EP9007 | 20010803 |

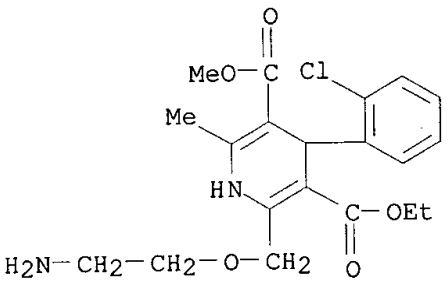
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2000-EP7533 A 20000803
OTHER SOURCE(S): MARPAT 136:172796

AB The present invention refers to a pharmaceutical compn. suitable for the transdermal or transmucosal administration of one or more active agents, in form of a gel or a soln., comprising as a permeation enhancers a combination of: a) satd. fatty alc. of formula Me(CH2)nCH2OH or satd. fatty acid Me(CH2)nCH2COOH wherein n = 8-12, most preferably 10, or unsatd. fatty alc. or fatty acid: Me[CnH2(n-1)]OH or Me[CnH2(n-1)]COOH wherein n = 8-22, b) a ternary vehicle or **carrier** consisting of a C1-C4 alkanol, a polyalc. in particular propylene glycol and water, c) optionally also a monoalkyl ether of diethylene glycol. A gel was prepd. contg. testosterone, lauryl alc., Transcutol P, propylene glycol, ethanol, distd. water, Carbopol 980, triethanolamine, and di-Na EDTA.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. for transdermal and/or transmucosal administration of active compds. that ensures adequate therapeutic levels)

RN 88150-42-9 HCAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:71857 HCAPLUS
DOCUMENT NUMBER: 136:139826
TITLE: Selective cyclooxygenase-2 inhibitors and vasomodulator compounds for generalized pain and headache pain
INVENTOR(S): Hassan, Fred; Forbes, James C.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002005799 | A2 | 20020124 | WO 2001-US22103 | 20010713 |

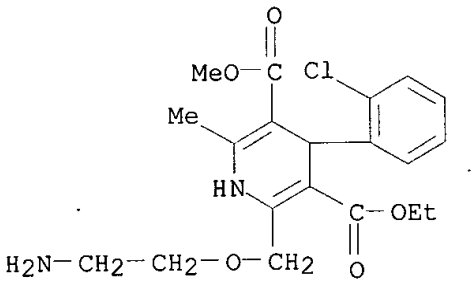
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-218101P P 20000713
US 2001-284248P P 20010417
US 2001-296196P P 20010606

OTHER SOURCE(S): MARPAT 136:139826

AB A therapeutic combination useful in the treatment, amelioration, prevention, or delay of pain comprising a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator, and a pharmaceutically acceptable excipient, **carrier**, or diluent, the cyclooxygenase-2 inhibitor and vasomodulator each being present in an amt. effective to contribute to the treatment, prevention, or delay of pain. Thus, capsules contained celecoxib 200, Labrasol 280, diethylene glycol monoethyl ether 280, and propylene glycol laurate 140/capsule.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitors and vasomodulators for generalized pain and headache pain treatment)
RN 88150-42-9 HCAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:396644 HCAPLUS
DOCUMENT NUMBER: 135:24671
TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
INVENTOR(S): Patel, Manesh V.; Chen, Feng-jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001037808 | A1 | 20010531 | WO 2000-US32255 | 20001122 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6248363 | B1 | 20010619 | US 1999-447690 | 19991123 |

PRIORITY APPLN. INFO.: US 1999-447690 A 19991123

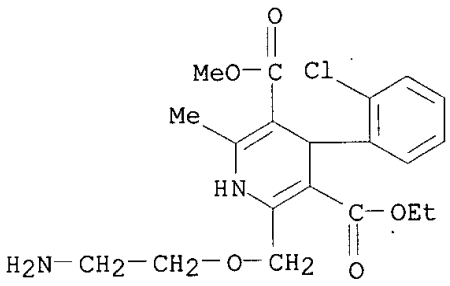
AB The present invention provides solid pharmaceutical compns. for improved delivery of a wide variety of pharmaceutical active ingredients contained therein or sep. administered. In one embodiment, the solid pharmaceutical compn. includes a solid **carrier**, the solid **carrier** including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of pharmaceutical active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides. In another embodiment, the solid pharmaceutical compn. includes a solid **carrier**, the solid **carrier** being

formed of different combinations of pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides. The compns. of the present invention can be used for improved delivery of hydrophilic or hydrophobic pharmaceutical active ingredients, such as drugs, nutritionals, cosmeceuticals and diagnostic agents. A compn. contained glyburide 1, PEG 40 stearate 33, glycerol monolaurate 17, and nonpareil seed 80 g.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solid carriers for improved delivery of active ingredients in pharmaceutical compns.)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338762 HCAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001032928 | A2 | 20010510 | WO 2000-US30474 | 20001103 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

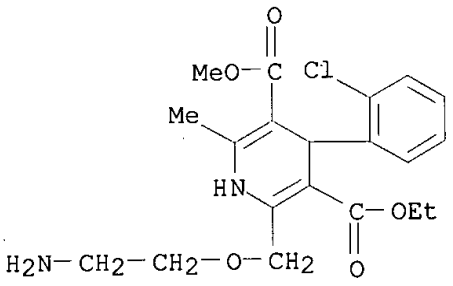
PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

IT **88150-42-9, Amlodipine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



L5 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:195203 HCAPLUS

DOCUMENT NUMBER: 134:202702

TITLE: Valsartan-calcium channel blocker combination composition and treatment for cardiovascular and other conditions

INVENTOR(S): Webb, Randy Lee; de Gasparo, Marc

PATENT ASSIGNEE(S): Novartis A.-G., Switz.

SOURCE: U.S., 5 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| US 6204281 | B1 | 20010320 | US 1999-349654 | 19990708 |
| US 2001049384 | A1 | 20011206 | US 2001-757413 | 20010109 |

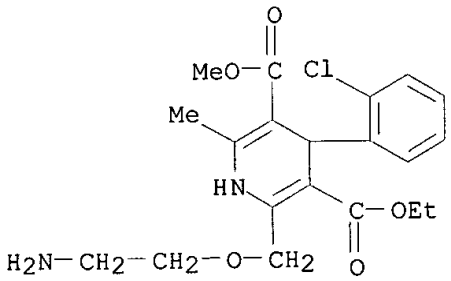
PRIORITY APPLN. INFO.: US 1998-155262P P 19980710
US 1999-349654 A3 19990708

AB A method is provided for the treatment or prevention of a condition or disease selected from hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae, supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amt. of combination of (i) the AT1 antagonist valsartan, or a pharmaceutically acceptable salt thereof, and (ii) a calcium channel blocker, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable **carrier** to a mammal in need of such treatment. A pharmaceutical combination compn. is also provided.

IT **88150-42-9, Amlodipine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(valsartan-calcium channel blocker combination compn. and treatment for cardiovascular and other conditions)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)




REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2002 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 2000:725436 HCAPLUS |
| DOCUMENT NUMBER: | 133:301171 |
| TITLE: | Compositions and methods for improved delivery of ionizable hydrophobic therapeutic agents |
| INVENTOR(S): | Chen, Feng-jing; Patel, Manesh V. |
| PATENT ASSIGNEE(S): | Lipocine, Inc., USA |
| SOURCE: | PCT Int. Appl., 99 pp.<br>CODEN: PIXXD2 |

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000059475 | A1 | 20001012 | WO 2000-US7342 | 20000316 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6383471 | B1 | 20020507 | US 1999-287043 | 19990406 |
| EP 1165048 | A1 | 20020102 | EP 2000-916547 | 20000316 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |

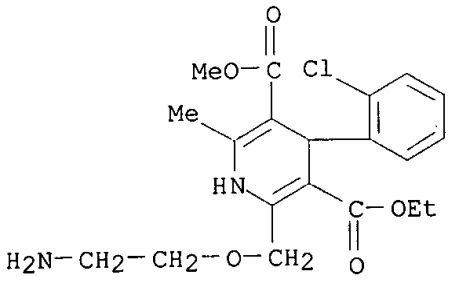
PRIORITY APPLN. INFO.: US 1999-287043 A 19990406
WO 2000-US7342 W 20000316

AB The present invention is directed to a pharmaceutical compn. including a hydrophobic therapeutic agent having at least one ionizable functional group, and a **carrier**. The **carrier** includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of prepg. such compns. by providing a compn. of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compns. of the invention are particularly suitable for use in oral dosage forms. A **carrier** contg. concd. phosphoric acid 0.025, Tween-20 0.3, Arlacel 186 0.2, sodium taurocholate 0.15, propylene glycol 0.3 g was formulated. Itraconazole was included in the **carrier** at 30 mg/mL for testing the stability of the itraconazole soln. upon diln. in simulated gastric fluid.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. hydrophobic therapeutic agents and carriers contg. ionizing agents and surfactants and triglycerides)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)




REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:608551 HCAPLUS
DOCUMENT NUMBER: 133:213151
TITLE: Pharmaceutical compositions and methods for improved delivery of hydrophobic therapeutic agents
INVENTOR(S): Patel, Manesh V.; Chen, Feng-Jing
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

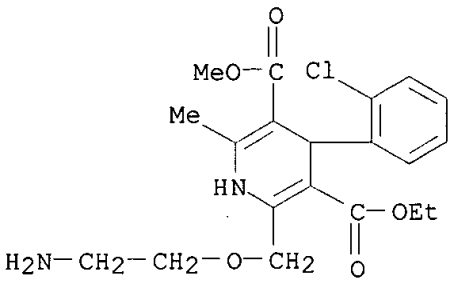
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000050007 | A1 | 20000831 | WO 2000-US165 | 20000105 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6294192 | B1 | 20010925 | US 1999-258654 | 19990226 |
| EP 1158959 | A1 | 20011205 | EP 2000-901394 | 20000105 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 2002012680 | A1 | 20020131 | US 2001-898553 | 20010702 |

PRIORITY APPLN. INFO.: US 1999-258654 A 19990226
WO 2000-US165 W 20000105

AB The present invention relates to triglyceride-free pharmaceutical compns. for delivery of hydrophobic therapeutic agents. Compns. of the present invention include a hydrophobic therapeutic agent and a **carrier**, where the **carrier** is formed from a combination of a hydrophilic surfactant and a hydrophobic surfactant. Upon diln. with an aq. solvent, the compn. forms a clear, aq. dispersion of the surfactants contg. the therapeutic agent. The invention also provides methods of treatment with hydrophobic therapeutic agents using these compns. A pharmaceutical compn. contained cyclosporin 0.14, Cremophor RH-40 0.41, Arlacel186 0.29, sodium taurocholate 0.26, and propylene glycol 0.46 mg.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and methods for improved delivery of hydrophobic therapeutic agents)

RN 88150-42-9 HCAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:531583 HCAPLUS
DOCUMENT NUMBER: 133:140256
TITLE: Controlled release pharmaceutical dosage forms containing polymers
INVENTOR(S): Ayer, Atul D.; Lam, Andrew; Magruder, Judy A.; Hamel, Lawrence G.; Wong, Patrick S. L.
PATENT ASSIGNEE(S): Alza Corporation, USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

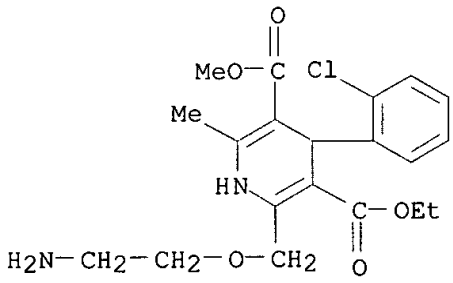
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6096339 | A | 20000801 | US 1997-826642 | 19970404 |

AB The invention disclosed pertains to a controlled-release dosage form comprising a drug and a pharmaceutical **carrier** (a hydrophilic polymer) of the right particle size. The drug has a particle size of <150 .mu.m and the polymer has the size <250 .mu.m.

IT **88150-42-9, Amlodipine**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release pharmaceutical dosage forms contg. polymers)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS

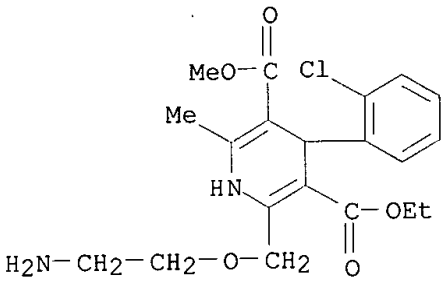
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:109766 HCAPLUS
DOCUMENT NUMBER: 133:37955
TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-.alpha. on endothelial cells
AUTHOR(S): Cominacini, Luciano; Pasini, Anna Fratta; Pastorino, Antonio M.; Garbin, Ulisse; Davoli, Anna; Rigoni, Anna; Campagnola, Mario; Tosetti, Maria L.; Rossato, Paolo; Gaviraghi, Giovanni
CORPORATE SOURCE: Department of Internal and Surgical Sciences, University of Verona, Verona, Italy
SOURCE: Journal of Hypertension (1999), 17(12, Pt. 2), 1837-1841
CODEN: JOHYD3; ISSN: 0263-6352
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lacidipine has already been demonstrated to reduce the expression of some adhesion mols. induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this mol., or belongs to other dihydropyridinic compds. (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. The compds. were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-d. lipoprotein as a **carrier**. The drug concns. in HUVECs were measured by mass spectrometry. Human recombinant tumor necrosis factor-.alpha. was then incubated with HUVECs for 7 h at 37.degree. for adhesion mol. expression. The cellular amt. of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, resp. Lacidipine, at any concn., detd. a dose-dependent significant decrease of the expression of intercellular adhesion mol.-1 (ICAM-1), vascular cell adhesion mol.-1 (VCAM-1) and E-selectin. Lercanidipine and **amlodipine** detd. variable decreases of adhesion mols. at the intermediate and highest concns. Nimodipine and nifedipine detd. no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concn. detg. the 50% redn. of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion mols. considered. It is concluded that the effect of the DHPs used in this study on adhesion mol. expression is detd. first by their lipophilicity and then by their intrinsic antioxidant activity.

IT **88150-42-9, Amlodipine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of different dihydropyridine calcium antagonists on expression of adhesion mols. induced by TNF-.alpha. on endothelial cells)

RN 88150-42-9 HCAPLUS
CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:53366 HCAPLUS
DOCUMENT NUMBER: 132:88204
TITLE: Method of treatment and pharmaceutical composition using valsartan-calcium channel blocker combination
INVENTOR(S): De Gasparo, Marc; Webb, Randy Lee
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000002543 | A2 | 20000120 | WO 1999-EP4842 | 19990709 |
| WO 2000002543 | A3 | 20000629 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9950349 | A1 | 20000201 | AU 1999-50349 | 19990709 |
| BR 9912021 | A | 20010403 | BR 1999-12021 | 19990709 |
| EP 1096932 | A2 | 20010509 | EP 1999-934647 | 19990709 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| NO 2001000113 | A | 20010309 | NO 2001-113 | 20010108 |

PRIORITY APPLN. INFO.: US 1998-113893 A 19980710
WO 1999-EP4842 W 19990709

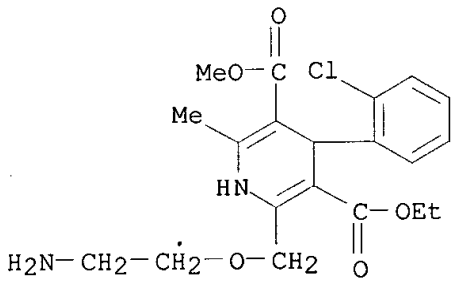
AB A method is provided for the treatment or prevention of a condition or disease selected from hypertension, (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, myocardial infarction and its sequelae supraventricular and ventricular arrhythmias, atrial fibrillation or atrial flutter, atherosclerosis, angina (whether stable or unstable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, hypertension in patients with NIDDM, secondary aldosteronism, primary and secondary

pulmonary hyperaldosteronism, primary and pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), and stroke, comprising administering a therapeutically effective amt. of combination of (i) the AT1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a calcium channel blocker or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable **carrier** to a mammal in need of such treatment. A corresponding pharmaceutical combination compn. is also provided.

IT **88150-42-9, Amlodipine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(valsartan-calcium channel blocker pharmaceutical combination)

RN 88150-42-9 HCAPLUS

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester (9CI) (CA INDEX NAME)

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L6 22 SEA L5

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L6 ANSWER 1 OF 22 MEDLINE
ACCESSION NUMBER: 2001678283 MEDLINE
DOCUMENT NUMBER: 21580729 PubMed ID: 11724204
TITLE: The effects of dihydropyridine and phenylalkylamine calcium antagonist classes on autonomic function in hypertension: the VAMPHYRE study.
AUTHOR: Lefrandt J D; Heitmann J; Sevre K; Castellano M; Hausberg M; Fallon M; Fluckiger L; Urbigkeit A; Rostrup M; Agabiti-Rosei E; Rahn K H; Murphy M; Zannad F; de Kam P J; van Roon A M; Smit A J
CORPORATE SOURCE: University Hospital of Groningen, The Netherlands.. j.d.lefrandt@int.azg.nl
SOURCE: AMERICAN JOURNAL OF HYPERTENSION, (2001 Nov) 14 (11 Pt 1) 1083-9.
Journal code: 8803676. ISSN: 0895-7061.
PUB. COUNTRY: United States
(CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011129
Last Updated on STN: 20020307
Entered Medline: 20020306

AB The aim of the present study was to compare the effects of a long-acting dihydropyridine (**amlodipine**) and a nondihydropyridine (verapamil) on autonomic function in patients with mild to moderate hypertension. A total of 145 patients with a diastolic blood pressure (BP) between 95 and 110 mm Hg received 8 weeks of verapamil sustained release (240 mg) and **amlodipine** (5 mg) in a prospective randomized, double blind, cross-over study, both after 4 weeks of placebo. The 24-h autonomic balance was measured by analysis of 24-h heart rate variability and short-term autonomic control of BP by baroreflex sensitivity measurements. Plasma norepinephrine was sampled at rest. Blood pressure was equally reduced from 153/100 mm Hg to 139/91 mm Hg with verapamil and 138/91 mm Hg with **amlodipine**, P = .50/.59. The low- to high-frequency ratio (LF/HF), reflecting sympathovagal balance, was higher with **amlodipine** than with verapamil (4.66 v 4.10; P = .001). Baroreflex function was improved by both treatments; however, baroreflex sensitivity (BRS) was significantly higher with verapamil than with **amlodipine** (8.47 v 8.06 msec/mm Hg; P = .01). Plasma norepinephrine (NE) level was higher with **amlodipine** than with verapamil (1.59 v 1.32 nmol/L; P < .0001). **Amlodipine** induces a shift in sympathovagal balance, as measured by heart rate variability indices and plasma NE, toward sympathetic predominance compared with vagal predominance with verapamil. Short-term autonomic control of BP, as assessed by BRS, is more effectively improved by verapamil than by **amlodipine**. These contrasting effects on autonomic function suggest that the nondihydropyridine calcium antagonist verapamil may have additional beneficial effects beyond lowering BP compared with the dihydropyridine **amlodipine**.

L6 ANSWER 2 OF 22 MEDLINE
ACCESSION NUMBER: 2000166643 MEDLINE
DOCUMENT NUMBER: 20166643 PubMed ID: 10703877
TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-alpha on endothelial cells.
AUTHOR: Cominacini L; Pasini A F; Pastorino A M; Garbin U; Davoli A; Rigoni A; Campagnola M; Tosetti M L; Rossato P; Gaviraghi G
CORPORATE SOURCE: Department of Internal and Surgical Sciences, University of Verona, Italy.. comina@medicinad.univr.it
SOURCE: JOURNAL OF HYPERTENSION, (1999 Dec) 17 (12 Pt 2) 1837-41. Journal code: IEW; 8306882. ISSN: 0263-6352.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB OBJECTIVE: Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on

endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. DESIGN AND METHODS: The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor-alpha was then incubated with HUVECs for 7 h at 37 degrees C for adhesion molecule expression. RESULTS: The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin ($P < 0.01$). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered ($P < 0.01$). CONCLUSIONS: It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity.

L6 ANSWER 3 OF 22 MEDLINE
ACCESSION NUMBER: 96021088 MEDLINE
DOCUMENT NUMBER: 96021088 PubMed ID: 7575651
TITLE: The low-affinity dihydropyridine receptor and Na+/Ca2+ exchanger are associated in adrenal medullary mitochondria.
AUTHOR: Palmero M; Gutierrez L M; Hidalgo M J; Reig J A; Ballesta J J; Viniegra S
CORPORATE SOURCE: Departamento de Neuroquimica, Universidad de Alicante, Spain.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1995 Sep 7) 50 (6) 879-83. Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 20000303
Entered Medline: 19951031

AB The effect of Ca2+ channel-acting drugs on bovine adrenal mitochondria Ca2+ movements was investigated. Mitochondrial Ca2+ uptake is performed by an energy-driven Ca2+ uniporter with a Km of 20.9 +/- 3.2 microM and Vmax of 148.1 +/- 7.2 nmol 45Ca2+ min-1 mg-1. Ca2+ release is performed through an Na+/Ca2+ antiporter with a Km for Na+ of 4.2 +/- 0.5 mM, a Vmax of 7.5 +/- 0.4 nmol 45Ca2+ min-1 mg-1, and a Hill coefficient of 1.4 +/- 0.2 Ca2+ efflux through the mitochondrial Na+/Ca2+ exchanger was inhibited by several dihydropyridines (nitrendipine, felodipine, nimodipine, (+)isradipine) and by the benzothiazepine diltiazem with similar potencies. In contrast, neither CGP 28392, Bay-K-8644, **amlodipine** , nor verapamil had any effect on Ca2+ efflux. Nitrendipine at 20 microM modified neither the Km nor the Hill coefficient for Na+, whereas the Vmax was reduced to 2.9 nmol 45Ca2+ min-1 mg-1, thus demonstrating noncompetitive modulation of the Na+/Ca2+ exchanger. None of the Ca2+ channel-acting drugs assayed at 100 microM affected Ca2+ influx through the uniporter. Ca2+ channel blockers inhibited the Na+/Ca2+ antiporter and

displaced the specific binding of [3H]nitrendipine to intact mitochondria with Ki values similar to the IC50s obtained for the inhibition of the Ca2+ efflux. Ca2+ channel-acting drugs that did not inhibit the Na+/Ca2+ exchanger (**amlodipine**, CGP 28392, Bay-K-9644, and verapamil, at concentrations of 100 microM or higher) had no effect on [3H]nitrendipine binding. These results suggest that the adrenomedullary mitochondrial dihydropyridine receptor is associated with the Na+/Ca2+ exchanger.

L6 ANSWER 4 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:121779 BIOSIS
DOCUMENT NUMBER: PREV200000121779
TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-alpha on endothelial cells.
AUTHOR(S): Cominacini, Luciano (1); Pasini, Anna Fratta; Pastorino, Antonio M.; Garbin, Ulisse; Davoli, Anna; Rigoni, Anna; Campagnola, Mario; Tosetti, Maria L.; Rossato, Paolo; Gaviraghi, Giovanni
CORPORATE SOURCE: (1) Istituto di Semeiotica e Nefrologia Medica, Ospedale Policlinico, 37134, Verona Italy
SOURCE: Journal of Hypertension, (Dec., 1999) Vol. 17, No. 12 part 2, pp. 1837-1841.
ISSN: 0263-6352.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objective Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. Design and methods The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor-alpha was then incubated with HUVECs for 7 h at 37degreeC for adhesion molecule expression. Results The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin ($P < 0.01$). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1, VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered ($P < 0.01$). Conclusions It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity.

L6 ANSWER 5 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001075021 EMBASE
TITLE: Chromatographic retention of drug molecules on immobilised liposomes prepared from egg phospholipids and from chemically pure phospholipids.
AUTHOR: Osterberg T.; Svensson M.; Lundahl P.
CORPORATE SOURCE: T. Osterberg, Preformulation Sciences, R and D Pharmacia

Corporation, SE-112 87 Stockholm, Sweden
SOURCE: European Journal of Pharmaceutical Sciences, (2001) 12/4 (427-439).
Refs: 61
ISSN: 0928-0987 CODEN: EPSCED
PUBLISHER IDENT.: S 0928-0987(00)00183-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The partitioning of a chemically diverse set of drugs into liposomes was studied by immobilised liposome chromatography (ILC). For this purpose liposomes composed of (i) purified egg phospholipids (EPL), (ii) synthetic phosphatidylcholine (PC), (iii) PC-synthetic phosphatidylethanolamine (PE) 80:20 (mol/mol) and (iv) PC-synthetic phosphatidylserine (PS) 80:20 (mol/mol) were immobilised in gel beads by freeze-thawing. The drug partitioning was assessed from the retention volume, which was expressed as a capacity factor, K(s), normalised with respect to the amount of immobilised phospholipid. The drug retention on EPL, PC and PC-PE liposomes was very similar, whereas the negatively charged PC-PS liposomes increased the retention of positively charged and decreased retention of negatively charged drugs. The partitioning of drugs on liposome columns (log K(s)) versus their octanol-water partitioning (log P(oct)) showed three separate rectilinear relationships, depending on the charge of the compound (neutral, positive, or negative). Statistical analysis (ANCOVA) proved that the lines had similar slopes. Repeated analysis of four reference compounds showed a low variation (<0.12 log units) over time (about 250 days). A close relationship was observed between the drug retention in short EPL columns with a low content of phospholipids and the retention in longer standard EPL columns. The short 'quick screen bilayer columns' permit analysis of highly lipophilic compounds within 30 min and are thus applicable for medium-throughput screening in drug discovery settings. A very strong rectilinear relationship (r(2)=0.95, n=13) between log K(s) (EPL) and published liposome partitioning data (log D(mem)) confirmed that the ILC drug retention reflects the drug partitioning into the lipid bilayers. A moderate to fair rectilinear relationship was observed between the normalised retention on PC, PC-PE and EPL liposomes (r(2)=0.79, 0.86 and 0.85, respectively, n=24) and corresponding published log k'(IAM) data obtained on immobilised artificial membrane (IAM) columns. Transport across Caco-2 cell monolayers (log P(c)) showed curvilinear relationships with log K(s), log k'(IAM), log P(oct) and log D(oct). The drug fraction absorbed in humans showed a similar relationship to log K(s) values as to surface plasmon resonance signals representing drug-liposome interaction (Danelian et al., 2000 J Med Chem, 43, 2083-2086). Copyright .COPYRGT. 2001 Elsevier Science B.V.

L6 ANSWER 6 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000198330 EMBASE
TITLE: Comparative effects of different dihydropyridines on the expression of adhesion molecules induced by TNF-.alpha. on endothelial cells.
AUTHOR: Cominacini L.; Pasini A.F.; Pastorino A.M.; Garbin U.; Davoli A.; Rigoni A.; Campagnola M.; Tosetti M.L.; Rossato P.; Gaviraghi G.
CORPORATE SOURCE: Dr. L. Cominacini, Ist. Semeiotica e Nefrologia Medica, Ospedale Policlinico, 37134 Verona, Italy.
comina@medicinad.univr.it

SOURCE: Journal of Hypertension, (1999) 17/12 II (1837-1841).
Refs: 42
ISSN: 0263-6352 CODEN: JOHYD3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective. Lacidipine has already been demonstrated to reduce the expression of some adhesion molecules induced by pro-oxidant signals on endothelial cells. In order to verify if this effect is a peculiarity of this molecule, or belongs to other dihydropyridinic compounds (DHPs), the activity of lacidipine was compared with that of lercanidipine, **amlodipine**, nimodipine and nifedipine. Design and methods. The compounds were incorporated in human umbilical vein endothelial cells (HUVECs) using native low-density lipoprotein as a **carrier**. The drug concentrations in HUVECs were measured by mass spectrometry. Human recombinant tumour necrosis factor-.alpha. was then incubated with HUVECs for 7 h at 37.degree.C for adhesion molecule expression. Results. The cellular amount of lacidipine, lercanidipine and **amlodipine** was similar, while nimodipine and nifedipine were almost undetectable or undetectable, respectively. Lacidipine, at any concentration, determined a dose-dependent significant decrease of the expression of intercellular adhesion molecule-1 (ICAM-1) ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) VCAM-1 and E-selectin ($P < 0.01$). Lercanidipine and **amlodipine** determined variable decreases of adhesion molecules at the intermediate and highest concentrations. Nimodipine and nifedipine determined no effect on ICAM-1,VCAM-1 and E-selectin. The lowest IC50, i.e. the concentration determining the 50% reduction of ICAM-1, VCAM-1 and E-selectin expression was obtained with lacidipine for all the adhesion molecules considered ($P < 0.01$). Conclusions. It is concluded that the effect of the DHPs used in this study on adhesion molecule expression is determined first by their lipophilicity and then by their intrinsic antioxidant activity. (C) Lippincott Williams and Wilkins.

L6 ANSWER 7 OF 22 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 96052003 EMBASE
DOCUMENT NUMBER: 1996052003

TITLE: .alpha.2-Adrenoceptor activation increases calcium channel currents in single vascular smooth muscle cells isolated from human omental resistance arteries.

AUTHOR: Hughes A.D.; Parkinson N.A.; Wijetunge S.
CORPORATE SOURCE: Department of Clinical Pharmacology, Imperial Coll. of Science Technology, South Wharf Road,London W2 1NY, United Kingdom

SOURCE: Journal of Vascular Research, (1996) 33/1 (25-31).
ISSN: 1018-1172 CODEN: JVREE
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Single cells were freshly isolated from human omental resistance arteries using an enzymatic dispersion technique. Calcium channel currents (I(Ba)) were recorded using whole cell voltage clamp techniques with Ba2+ as the charge **carrier**. BHT 933, a selective .alpha.2-adrenoceptor

agonist, increased I(Ba). The effect of BHT 933 was reversible following washout. The action of BHT 933 was blocked by yohimbine. Pretreatment of tissues with pertussis toxin for 18 h or inclusion of GDP-.beta.-S in the intracellular patch pipette solution also prevented the BHT 933-induced rise in I(Ba), but had no effect on I(Ba) in the absence of BHT 933. Activation of .alpha.2-adrenoceptors in human vascular smooth muscle cells increases I(Ba) by a mechanism involving a pertussis toxin-sensitive G protein.

L6 ANSWER 8 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-218972 [28] WPIDS
DOC. NO. CPI: C2002-067112
TITLE: Therapeutic compositions comprising excess enantiomer of **amlodipine** useful for the treatment of a condition for which a vascular NO-releasing agent and an anti-hypertensive is indicated.
DERWENT CLASS: B02 B03
INVENTOR(S): CHAHWALA, S B; DODD, M G; HUMPHREY, M J
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD; (CHAH-I) CHAHWALA S B; (DODD-I) DODD M G; (HUMP-I) HUMPHREY M J
COUNTRY COUNT: 29
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| EP 1181932 | A2 | 20020227 | (200228)* | EN | 8 |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR | | | | | |
| CA 2355493 | A1 | 20020223 | (200228) | EN | |
| US 2002045648 | A1 | 20020418 | (200228) | | |
| BR 2001003434 | A | 20020326 | (200229) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| EP 1181932 | A2 | | EP 2001-306940 | 20010815 |
| CA 2355493 | A1 | | CA 2001-2355493 | 20010821 |
| US 2002045648 | A1 | Provisional | US 2000-237168P | 20001002 |
| | | | US 2001-930330 | 20010815 |
| BR 2001003434 | A | | BR 2001-3434 | 20010817 |

PRIORITY APPLN. INFO: GB 2000-20842 20000823
AN 2002-218972 [28] WPIDS
AB EP 1181932 A UPAB: 20020502
NOVELTY - A pharmaceutical composition comprises the R(+) enantiomer of **amlodipine** or its salt, the S(-) enantiomer of **amlodipine** or its salt and an excipient, **carrier** or diluent. The enantiomers are present in a ratio by weight based on free base of R(+) enantiomer:(S(-) enantiomer of greater than 1:1.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) preparation of the composition;

(2) a pharmaceutical composition comprising an NO-releasing amount the R(+) enantiomer of **amlodipine** or its salt, an NO-inducing amount of an ACE inhibitor and an excipient, **carrier** or diluent;

(3) a pharmaceutical composition comprising an NO-releasing amount the R(+) enantiomer of **amlodipine** or its salt, an NO-potentiating amount of an PDE5 inhibitor and an excipient, **carrier** or diluent.

ACTIVITY - Hypotensive.
MECHANISM OF ACTION - None given.
USE - The composition is used for the treatment of a condition for which a vascular NO-releasing agent and an anti-hypertensive is indicated.
ADVANTAGE - The compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel blocking activity and their ability to release vascular nitric oxide.
Dwg.0/0

L6 ANSWER 9 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-195775 [25] WPIDS
CROSS REFERENCE: 2002-195783 [14]
DOC. NO. CPI: C2002-060502
TITLE: Therapeutic combination for treatment, prevention or delay of pain (especially headache) comprises a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator and a **carrier**.
DERWENT CLASS: B02
INVENTOR(S): FORBES, J C; HASSAN, F
PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP
COUNTRY COUNT: 96
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2002005799 | A2 | 20020124 | (200225)* | EN | 217 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2002005799 | A2 | WO 2001-US22103 | 20010713 |

PRIORITY APPLN. INFO: US 2001-296196P 20010606; US 2000-218101P 20000713; US 2001-284248P 20010417
AN 2002-195775 [25] WPIDS
CR 2002-195783 [14]
AB WO 200205799 A UPAB: 20020508
NOVELTY - Therapeutic combination for treatment, prevention or delay of pain comprises a high energy form of a selective cyclooxygenase-2 inhibitor, a vasomodulator and a **carrier**.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an orally deliverable comprising a selective cyclooxygenase-2 inhibitor in rapid release form, and a xanthine compound to treat headache pain; and
(2) a method of treatment of pain by administering a high energy form of a selective cyclooxygenase-2 inhibitor and a vasomodulator.
ACTIVITY - Analgesic; Antimigraine.
MECHANISM OF ACTION - Vasodilator; Vasoconstrictor; Cyclooxygenase-2 (COX-2) inhibitor; 5 HT1 receptor inhibitor.
The combined active agents bind to 5 HT1 receptors with an IC50 of at

least 250, 500, 750, 1000, 5000 or 10000 nM (claimed). In vivo bioavailability of a test composition (A) was compared to a Celebrex (RTM) capsule (B) and a celecoxib suspension (C). Cmax for (A), (B) and (C) was 2061, 621 and 804 ng/ml respectively. Tmax for (A), (B) and (C) was 1.03, 2.15 and 0.97 hours respectively. (A), (B) and (C) had AUC values of 7593, 5060 and 4892 ng/ml.hour respectively.

USE - To treat pain (especially headache pain (claimed).

ADVANTAGE - The cyclooxygenase-2 inhibitor can be formulated in 2 fractions to provide instant effect (as solid particles) and in solution to provide sustained release.

Dwg.0/10

L6 ANSWER 10 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-138392 [18] WPIDS
DOC. NO. CPI: C2002-042591
TITLE: New pharmaceutical composition useful for the treatment of hypertension comprises deuterated S(-) **amlodipine** or its salt.
DERWENT CLASS: B03
INVENTOR(S): FOSTER, R T
PATENT ASSIGNEE(S): (ISOT-N) ISOTECHNIKA INC
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 6333342 | B1 | 20011225 | (200218)* | | 10 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| US 6333342 | B1 Provisional | US 1998-107007P | 19981104 |
| | | US 1999-433963 | 19991104 |

PRIORITY APPLN. INFO: US 1998-107007P 19981104; US 1999-433963 19991104
AN 2002-138392 [18] WPIDS
AB US 6333342 B UPAB: 20020319

NOVELTY - A pharmaceutical composition comprises deuterated pure S(-)isomer of **amlodipine** or its salt and a **carrier**.

DETAILED DESCRIPTION - A pharmaceutical composition comprises deuterated S(-)**amlodipine** of formula (I) or its salt and a **carrier**.

R and R1 = H or deuterium;

asterisk = chiral carbon.

At least one R and R1 are deuterium.

An INDEPENDENT CLAIM is also included for a compound of formula (I).

ACTIVITY - Hypotensive; antianginal; cerebroprotective; antiarrhythmic; nootropic; cardiant; virucide; thrombolytic; antiarteriosclerotic; antimigraine; vasotropic; neuroprotective; antiasthmatic; antiemetic; nephrotropic.

MECHANISM OF ACTION - Calcium channel blocker; calcium channel antagonist.

Test details are given but no results are given.

USE - In the treatment of calcium channel blocking therapy e.g. hypertension, angina, cerebral ischemia, cerebral disorders, arrhythmia, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis,

atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury or acute renal failure (all claimed); Alzheimer's dementia, memory impairment, retinal ischemia, asthma, bronchospasm, Raynaud's phenomenon or cognitive disorders.

ADVANTAGE - The composition avoids concomitant liability of adverse effects associated with administration of racemic **amlodipine**. The composition avoids toxicities and adverse effects of racemic **amlodipine**. The composition results in clearer dose-related definitions of efficacy and improves therapeutic index. The composition reduces the probability of occurrence of hypertension.

Dwg.0/0

L6 ANSWER 11 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-121537 [16] WPIDS
CROSS REFERENCE: 2000-195440 [17]; 2002-226085 [28]
DOC. NO. NON-CPI: N2002-091167
DOC. NO. CPI: C2002-037169
TITLE: Coated stent for implantation in human vessels for treating occlusion in heart and kidney diseases, comprises calcium channel blocker carrying biodegradable **carrier** material coated on stent superstructure.
DERWENT CLASS: B05 D22 P32
INVENTOR(S): EASTERLING, W J
PATENT ASSIGNEE(S): (EAST-I) EASTERLING W J
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| US 2002004678 | A1 | 20020110 | (200216)* | | 3 |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| US 2002004678 | A1 | CIP of | US 1998-128103 | 19980803 |
| | | CIP of | US 2000-514796 | 20000228 |
| | | | US 2001-839572 | 20010420 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| US 2002004678 | A1 | CIP of | US 6031005 |

PRIORITY APPLN. INFO: US 2001-839572 20010420; US 1998-128103 19980803; US 2000-514796 20000228
AN 2002-121537 [16] WPIDS
CR 2000-195440 [17]; 2002-226085 [28]
AB US2002004678 A UPAB: 20020502

NOVELTY - A coated stent for implantation in human vessels, orifices and conduits for creating and sustaining openings and for preventing re-occlusion of the openings after implantation, comprises a stent superstructure, a biodegradable **carrier** material for coating the stent superstructure, and a calcium channel blocker agent carried by biodegradable **carrier** material.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for providing a re-occlusion resistant stent implantation to a human patient. The method involves selecting coated stent, and implanting into a human vessel, orifice or conduit.

ACTIVITY - Cardiant.
MECHANISM OF ACTION - Calcium channel blocker.
USE - For surgical implantation of stents, in treatment of arterial occlusion in heart disease, and ureteral occlusion in kidney disease or injury, for creating and sustaining opening, and for preventing re-occlusion of openings after implantation of the stent.
ADVANTAGE - The stent coated with a slow-release calcium channel blocker, interrupts the accumulation or deposition of fibrotic tissue, prevents or, at least, minimizes, processes leading to re-occlusion of the vessel or conduit, after implantation of the stent.
Dwg.0/0

L6 ANSWER 12 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-075043 [10] WPIDS
DOC. NO. CPI: C2002-022287
TITLE: Pharmaceutical pellet useful for inducing or maintaining sleep comprises homogenous mixture of rapidly acting hypnotic agent salt and pellet forming **carrier**.
DERWENT CLASS: B02
INVENTOR(S): LEMMENS, J M; PLATTEEUW, J J; VAN DALEN, F; VAN DEN HEUVEL, D J M
PATENT ASSIGNEE(S): (SYNT-N) SYNTHON BV
COUNTRY COUNT: 95
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2001078725 | A2 | 20011025 | (200210)* | EN | 41 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001050661 A 20011030 (200219)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2001078725 | A2 | WO 2001-NL299 | 20010412 |
| AU 2001050661 | A | AU 2001-50661 | 20010412 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2001050661 | A | Based on | WO 200178725 |

PRIORITY APPLN. INFO: US 2000-196939P 20000413
AN 2002-075043 [10] WPIDS
AB WO 200178725 A UPAB: 20020213
NOVELTY - Pharmaceutical pellet comprises a homogenous mixture of rapidly acting hypnotic agent or its salt and pellet forming **carrier**.
The pellet exhibits a specific dissolution profile under US Pharmacopoeia XXIII, Dissolution method I, in a basket apparatus at 37 deg. C in hydrochloric acid medium (0.01N) and at 100 r.p.m.
DETAILED DESCRIPTION - Pharmaceutical pellet comprises a homogenous mixture of rapidly acting hypnotic agent or its salt and pellet forming **carrier**. The pellet exhibits a dissolution profile under US

Pharmacopoeia XXIII, Dissolution method I, in a basket apparatus at 37degreesC in hydrochloric acid medium (0.01N) and at 100 r.p.m that includes 60% of the hypnotic agent being released from the pellet not earlier than 5 minutes from the start of the test.

An INDEPENDENT CLAIM is included for production of spherical pellets which comprises:

(1) combining a solvent (preferably water), a pharmaceutically active agent and/or its salt, and at least one pellet forming **carrier** to form a wet mixture;

(2) stirring and/or chopping the wet mixture to form monolithic, spherical wet pellets, and

(3) drying the wet pellets to form the pellets.

1) 2) 3) The solvent is wet combined by spraying.

ACTIVITY - Antiparkinsonian; Hypnotic.

MECHANISM OF ACTION - None given in source material.

USE - In a pharmaceutical unit dosage form for inducing or maintaining sleep or treating sleep disorders e.g. Parkinson's disease, parkinsonian syndromes and other disorders treatable by zolpidem.

ADVANTAGE - The pellet exhibits a modified release profile. The composition moderates the rapid release occurring in the commercial tablets so that initial over concentration of active agent in body fluids is minimized and the hypnotic action is reasonably delayed to overcome a shortage of sleep. A single dose of the pellet contains a lower amount of the active substance in comparison with that in the commercially available immediate release dosage form due to the advantageous release rates and consequently due to the expected advantageous blood plasma concentration profile which maintains the necessary concentration of zolpidem more effectively. Potential side effects of the hypnotic agent is decreased.

Dwg.0/4

L6 ANSWER 13 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2002-062005 [08] WPIDS
DOC. NO. CPI: C2002-017651
TITLE: Composition comprises a carboxyalkylether and an antihypertensive agent for the treatment of hypertension and cardiovascular disorders.
DERWENT CLASS: B05
INVENTOR(S): AUERBACH, B J; HITCHCOCK, K D; RYAN, M J
PATENT ASSIGNEE(S): (WARN) WARNER LAMBERT CO
COUNTRY COUNT: 86
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2001080847 | A2 | 20011101 | (200208)* | EN | 38 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AU BA BB BG BR BZ CA CN CO CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX MZ NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU ZA

AU 2001047658 A 20011107 (200219)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2001080847 | A2 | WO 2001-US9088 | 20010322 |
| AU 2001047658 | A | AU 2001-47658 | 20010322 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2001047658 A | Based on | WO 200180847 |

PRIORITY APPLN. INFO: US 2000-242280P 20001020; US 2000-199855P 20000426

AN 2002-062005 [08] WPIDS

AB WO 200180847 A UPAB: 20020204

NOVELTY - Composition (A) comprises a carboxyalkylether or its addition salt, an antihypertensive agent or its salt and a **carrier** or diluent.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a first composition comprising an antihypertensive agent or its salt, for use with a second composition comprising a carboxyalkylether or its salt, for achieving an antihypertensive and/or cardiovascular effect in a mammal and which shows a synergistic effect;

(2) a first composition comprising an carboxyalkylether or its salt, for use with a second composition comprising an antihypertensive agent or its salt, for managing cardiac risk in a mammal suffering an adverse cardiac event and which shows a synergistic effect;

(3) a first composition comprising an carboxyalkylether of formula (II) or its salt, for use with a second composition comprising an antihypertensive agent or its salt, for achieving an antihypertensive effect in a mammal suffering from hypertension and which shows a synergistic effect;

(4) a kit for achieving a therapeutic effect in a mammal comprising a carboxyalkylether or acid addition salt in a first unit dosage form, an antihypertensive agent or its salt in a second dosage form and a container for the first and second dosage forms;

(5) a method for treating hypertension comprising administering a compound of formula (I), (II) or 6,6'-oxybis(2,2-dimethylhexanoic acid) or their salts, preferably 6,6'-oxybis(2,2-dimethylhexanoic acid) monocalcium; and

(6) a method for preventing a stroke in a mammal comprising administering 6,6'-oxybis(2,2-dimethylhexanoic acid monocalcium.

n, m = 2-9;

R1-R4 = 1-6C alkyl, 1-6C alkenyl, 2-6C alkynyl; or

R1 + R2 + C and R3 + R3 + C = form carbocyclic ring with 3-6 carbons.

ACTIVITY - Hypotensive; Cardiant; Antiartherosclerotic; Antianginal; Cerebroprotective.

The antihypertensive effects of the carboxyalkylether compound 6,6'-oxybis(2,2-dimethylhexanoic acid) (CI-1027) alone and in combination with the antihypertensive agent quinapril (CI-906) were evaluated in male spontaneously hypertensive rats. CI-1027 monotherapy demonstrated a modest antihypertensive activity. Multiple day quinapril treatment when added to ongoing CI-1027 treatment was found to greatly potentate the antihypertensive response.

MECHANISM OF ACTION - ACE inhibitors; Calcium channel blockers; Angiotension-II receptor antagonists; beta -adrenergic receptor blockers; alpha -adrenergic receptor blockers.

USE - For the treatment of vascular diseases and preventing a stroke in mammals. (A) is used for treating hypertension, angina pectoris, cardiac risk, atherosclerosis, preferably slowing the progression of atheroplaques in the coronary arteries, carotid arteries or peripheral arterial system or causes regression of artherosclerotic plaques in coronary arteries (all claimed).

ADVANTAGE - The combination of the carboxyalkylether and the antihypertensive agent is synergistic.

Dwg.0/0

L6 ANSWER 14 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-648522 [74] WPIDS
DOC. NO. CPI: C2001-191411
TITLE: Treatment of normotensive animals with renal disease comprises use of calcium channel blockers optionally in the presence of a different hypotensive agent.
DERWENT CLASS: B03 B05 C02 C03
INVENTOR(S): FOSTER, A P
PATENT ASSIGNEE(S): (FOST-I) FOSTER A P; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD
COUNTRY COUNT: 95
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2001074390 | A2 | 20011011 | (200174)* | EN | 19 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW | | | | | |
| US 2001036954 | A1 | 20011101 | (200174) | | |
| AU 2001039510 | A | 20011015 | (200209) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2001074390 | A2 | WO 2001-IB518 | 20010328 |
| US 2001036954 | A1 Provisional | US 2000-198415P | 20000419 |
| | | US 2001-818403 | 20010327 |
| AU 2001039510 | A | AU 2001-39510 | 20010328 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2001039510 | A Based on | WO 200174390 |

PRIORITY APPLN. INFO: GB 2000-8332 20000404
AN 2001-648522 [74] WPIDS
AB WO 200174390 A UPAB: 20011217
NOVELTY - Use of calcium channel blockers optionally in the presence of a different class of hypotensive agent e.g. an agent that reduces the effect of endothelin and/or angiotensin to treat normotensive animals with renal disease is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) unit dosage forms comprising 0.1-0.4 mg or 0.8-1.5 mg **amlodipine**, an optional antihypertensive agent and a pharmaceutical/veterinary **carrier**, diluent or adjuvant; and

(2) a pack comprising unit dose (1) and instructions for the treatment of renal disease in normotensive animals.

ACTIVITY - Hypotensive; Nephrotropic.

Domesticated cats with normotensive chronic renal failure were treated with oral placebo or **amlodipine** (0.125-0.25 mg/kg/day). In the control group (10 cats), the mean glomerular filtration rate (GFR) decreased from 0.9 to 0.75 ml/minute/kg between 7 and 224 days post regime commencement. In the **amlodipine** group (10 cats) the GFR

increased from 0.76 to 0.83 ml/minute/kg over the same period.
MECHANISM OF ACTION - Calcium Channel blocker.
USE - Useful for treating renal diseases in normotensive animals, especially humans and companion animals e.g. dog, horse and domestic cat.
ADVANTAGE - Useful for all normotensive renal conditions.
Dwg.0/0

L6 ANSWER 15 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-391763 [42] WPIDS
DOC. NO. CPI: C2001-119392
TITLE: Pharmaceutical compositions, useful for treating diabetic complications, comprise aldose reductase inhibitor and non-ACE inhibiting anti-hypertensive agent.
DERWENT CLASS: B05
INVENTOR(S): MYLARI, B L
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC
COUNTRY COUNT: 29
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| EP 1106210 | A2 | 20010613 | (200142)* | EN | 13 |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR | | | | | |
| CA 2327575 | A1 | 20010607 | (200145) | EN | |
| BR 2000005765 | A | 20010717 | (200146) | | |
| JP 2001163805 | A | 20010619 | (200150) | | 15 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| EP 1106210 | A2 | EP 2000-310719 | 20001201 |
| CA 2327575 | A1 | CA 2000-2327575 | 20001205 |
| BR 2000005765 | A | BR 2000-5765 | 20001207 |
| JP 2001163805 | A | JP 2000-369434 | 20001205 |

PRIORITY APPLN. INFO: US 1999-169380P 19991207
AN 2001-391763 [42] WPIDS
AB EP 1106210 A UPAB: 20010726
NOVELTY - Pharmaceutical compositions comprising an aldose reductase inhibitor and a non ACE inhibitor anti-hypertensive agent are new.
DETAILED DESCRIPTION - Pharmaceutical compositions comprise:
(1) an aldose reductase inhibitor (ARI) (I), its prodrug or pharmaceutical salt;
(2) a non ACE inhibitor anti-hypertensive agent (II) its prodrug or pharmaceutical salt; and
(3) a **carrier**, vehicle or diluent (III).
An INDEPENDENT CLAIM is also included for a kit comprising dosage forms of (I) and (III), (II) and (III) and a container.
ACTIVITY - Anti-hypertensive; diuretic; vasodilator; anti-diabetic.
MECHANISM OF ACTION - Aldose reductase inhibitors; calcium channel blockers; angiotensin II receptor antagonists; beta adrenoceptor antagonists; neutral endopeptidease inhibitors; alpha adrenoceptor antagonists.
USE - Useful for treating or preventing diabetic complications including neuropathy, nephropathy, cardiomyopathy, retinopathy, cataracts and myocardial infarction.
Dwg.0/0

L6 ANSWER 16 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-147185 [13] WPIDS
DOC. NO. CPI: C2000-046042
TITLE: Nitrate salts of antihypertensive agents.
DERWENT CLASS: B02 B03
INVENTOR(S): DEL SOLDATO, P; DEL, S P
PATENT ASSIGNEE(S): (NICO-N) NICOX SA
COUNTRY COUNT: 75
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9967231 | A1 | 19991229 | (200013)* | EN | 77 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW | | | | | |
| W: AL AU BA BB BG BR CA CN CU CZ EE GE HR HU IL IN IS JP KP KR LK LR LT LV MG MK MN MX NO NZ PL RO RU SG SI SK TR TT UA US UZ VN YU ZA | | | | | |
| AU 9945139 | A | 20000110 | (200025) | | |
| EP 1087953 | A1 | 20010404 | (200120) | EN | |
| R: AT BE CH DE DK ES FI FR GB GR IE IT LI LT NL PT RO SE SI | | | | | |
| BR 9911305 | A | 20011023 | (200172) | | |
| CN 1315945 | A | 20011003 | (200205) | | |
| IT 1301759 | B | 20000707 | (200212) | | |
| HU 2001002719 | A2 | 20011228 | (200216) | | |
| KR 2001093631 | A | 20011029 | (200223) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9967231 | A1 | WO 1999-EP4138 | 19990615 |
| AU 9945139 | A | AU 1999-45139 | 19990615 |
| EP 1087953 | A1 | EP 1999-927990 | 19990615 |
| | | WO 1999-EP4138 | 19990615 |
| BR 9911305 | A | BR 1999-11305 | 19990615 |
| | | WO 1999-EP4138 | 19990615 |
| CN 1315945 | A | CN 1999-807516 | 19990615 |
| IT 1301759 | B | IT 1998-MI1408 | 19980619 |
| HU 2001002719 | A2 | WO 1999-EP4138 | 19990615 |
| | | HU 2001-2719 | 19990615 |
| KR 2001093631 | A | KR 2000-714179 | 20001214 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9945139 | A | Based on | WO 9967231 |
| EP 1087953 | A1 | Based on | WO 9967231 |
| BR 9911305 | A | Based on | WO 9967231 |
| HU 2001002719 | A2 | Based on | WO 9967231 |

PRIORITY APPLN. INFO: IT 1998-MI1408 19980619
AN 2000-147185 [13] WPIDS
AB WO 9967231 A UPAB: 20000313
NOVELTY - The nitrate salts of compounds with antihypertensive activity provide an improved therapeutic profile, and fewer side effects compared to known antihypertensive agents.
DETAILED DESCRIPTION - The nitrate salts of many antihypertensive agents are new. The agents include compounds of the following general

formulae:
XA1 = -COOH,
RA1 = -CH2OH,

The agents include Valsartan, Hydralazine, Minoxidil, Sildenafil, Zaprinast, Terazosin, Prazosin, Bucindolol, Bepridil, Clentiazem, Diltiazem, Fendiline, Gallopamil, Mibefradil, Prenylamine, Semotiadil, Terodiline, Verapamil, **Amlodipine**, Aranidipine, Barnidipine, Benedipine, Cilnidipine, Efonidipine, Elgodipine, Felodipine, Isradipine, Lacidipine, Lercanidipine, Manidipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Cinnarizine, Flunarizine, Lidoflazine, Lomerizine, Bencyclane, Etafenone, Fantofarone, Althiazide, Bendroflumethiazide, Benthiazide, Benzylhydrochlorothiazide, Buthiazide, Chlorothiazide, Chlortalidone, Cyclopenthiazide, Cyclothiazide, Epithiazide, Ethiazide, Fenquizone, Indapamide, Hydrochlorthiazide, Hydroflumethiazide, Methyclothiazide, Methycrane, Metolazone, Paraflutizide, Polythiazide, Quinethazone, Teclothiazide, Trichlormethiazide, Protheobromine, Teobromine, Aminometradine, Amisotradine, Amanozine, Amiloride, Chlorazanyl, Etozolin, Hydracarbazine, Muzolimine, Perhexiline, Triamterene, Bumetanide, Furosemide, Torasemide and Apomorphine, and analogues.

ACTIVITY - Antihypertensive.

MECHANISM OF ACTION - None given.

USE - For treating hypertension and cardiovascular disease (claimed).

ADVANTAGE - In many cases, the nitrate salt had greater antihypertensive effects and fewer side effects than its precursor. E.g. the effects on vasoconstriction in rats were: **Carrier** 100%, Sildenafil nitrate 25% and Sildenafil 68%; the arterial pressures in rats were: **Carrier** 170, Losartan nitrate 115, and Losartan 153 mm Hg; the incidences of gastric toxicity were: Control 50, Sildenafil 100; Sildenafil nitrate 20%.

Dwg.0/0

L6 ANSWER 17 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2000-064417 [06] WPIDS
DOC. NO. NON-CPI: N2000-050529
DOC. NO. CPI: C2000-018073
TITLE: Synergistic composition for treatment of arrhythmia, especially in patients with arterial fibrillation.
DERWENT CLASS: B03 B05 P34
INVENTOR(S): BILLING, C B; FALK, R H; FRIEDRICH, T
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (UYBO-N) UNIV BOSTON
COUNTRY COUNT: 28
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| EP 965341 | A2 | 19991222 | (200006)* | EN | 12 |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI | | | | | |
| JP 11335278 | A | 19991207 | (200008) | | 10 |
| CA 2270022 | A1 | 19991114 | (200017) | EN | |
| MX 9904460 | A1 | 20000701 | (200134) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| EP 965341 | A2 | EP 1999-303489 | 19990504 |
| JP 11335278 | A | JP 1999-132173 | 19990513 |
| CA 2270022 | A1 | CA 1999-2270022 | 19990427 |

MX 9904460 A1 MX 1999-4460 19990513

PRIORITY APPLN. INFO: US 1998-85496P 19980514
AN 2000-064417 [06] WPIDS
AB EP 965341 A UPAB: 20000203
NOVELTY - A pharmaceutical composition comprises:
(a) dofetilide (N-(4-(2-((2-(4-methanesulfonylamino-phenoxy)-ethyl)-methyl-amino)-ethyl)-phenyl) -methanesulfonamide);
(b) a calcium channel blocker; and
(c) a diluent or **carrier**.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising
(a) dofetilide and a **carrier** in a unit dosage;
(b) a calcium channel blocker and a **carrier** in a unit dosage; and
(c) a container for the dosage forms.
ACTIVITY - Antiarrhythmic.
Recurrence rate of arterial fibrillation was analyzed in a group of 264 patients. Patients dosed with the above combination showed reduced risk of recurrence (48 % cf. 38.1 %).
MECHANISM OF ACTION - Calcium channel blocker. Dofetilide is a selective inhibitor of the rapid component of the delayed rectifier potassium current which prolongs the action potential duration and the effective refractory period.
USE - Treatment of arrhythmia, especially in patients with arterial fibrillation, and with normal sinus rhythm maintained; or whose electrical remodeling of the atrium is inhibited prior to conversion to sinus rhythm; or who have been pre-treated with **amlodipine** prior to conversion to normal sinus rhythm with dofetilide and optional electrocardioversion to result in inhibition of recurrence of arterial fibrillation post cardioversion (all claimed).
ADVANTAGE - The quantities of dofetilide and **amlodipine** in the composition are insufficient alone for treatment of arrhythmia, however in combination a synergistic effect is achieved.
Dwg.0/0

L6 ANSWER 18 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-214611 [18] WPIDS
DOC. NO. CPI: C1999-063222
TITLE: Use of a synergistic combination of **amlodipine** and a statin compound for treating angina pectoris and atherosclerosis.
DERWENT CLASS: B03
INVENTOR(S): BUCH, J; SCOTT, R A D
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (PFIZ) PFIZER INC
COUNTRY COUNT: 84
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9911263 | A1 | 19990311 | (199918)* | EN | 55 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW | | | | | |
| W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW | | | | | |
| AU 9884585 | A | 19990322 | (199931) | | |
| ZA 9807843 | A | 20000426 | (200027) | | 55 |

NO 2000000999 A 20000228 (200029)
EP 1003507 A1 20000531 (200031) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO SE SI
CZ 2000000319 A3 20000816 (200048)
BR 9811558 A 20000822 (200050)
SK 2000000139 A3 20000814 (200051)
CN 1268054 A 20000927 (200067)
HU 2000003103 A2 20010131 (200118)
MX 2000002085 A1 20001001 (200158)
KR 2001022385 A 20010315 (200159)
JP 2001514224 W 20010911 (200167) 61
US 2002025981 A1 20020228 (200220)
AU 744982 B 20020307 (200229)

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9911263 | A1 | | WO 1998-IB1220 | 19980810 |
| AU 9884585 | A | | AU 1998-84585 | 19980810 |
| ZA 9807843 | A | | ZA 1998-7843 | 19980828 |
| NO 2000000999 | A | | WO 1998-IB1220 | 19980810 |
| | | | NO 2000-999 | 20000228 |
| EP 1003507 | A1 | | EP 1998-935246 | 19980810 |
| | | | WO 1998-IB1220 | 19980810 |
| CZ 2000000319 | A3 | | WO 1998-IB1220 | 19980810 |
| | | | CZ 2000-319 | 19980810 |
| BR 9811558 | A | | BR 1998-11558 | 19980810 |
| | | | WO 1998-IB1220 | 19980810 |
| SK 2000000139 | A3 | | WO 1998-IB1220 | 19980810 |
| | | | SK 2000-139 | 19980810 |
| CN 1268054 | A | | CN 1998-808465 | 19980810 |
| HU 2000003103 | A2 | | WO 1998-IB1220 | 19980810 |
| | | | HU 2000-3103 | 19980810 |
| MX 2000002085 | A1 | | MX 2000-2085 | 20000228 |
| KR 2001022385 | A | | KR 2000-700964 | 20000128 |
| JP 2001514224 | W | | WO 1998-IB1220 | 19980810 |
| | | | JP 2000-508366 | 19980810 |
| US 2002025981 | A1 | Provisional | US 1997-57555P | 19970829 |
| | | Cont of | US 2000-513889 | 20000225 |
| | | | US 2001-975765 | 20011010 |
| AU 744982 | B | | AU 1998-84585 | 19980810 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9884585 | A | Based on | WO 9911263 |
| EP 1003507 | A1 | Based on | WO 9911263 |
| CZ 2000000319 | A3 | Based on | WO 9911263 |
| BR 9811558 | A | Based on | WO 9911263 |
| HU 2000003103 | A2 | Based on | WO 9911263 |
| JP 2001514224 | W | Based on | WO 9911263 |
| AU 744982 | B | Previous Publ. | AU 9884585 |
| | | Based on | WO 9911263 |

PRIORITY APPLN. INFO: US 1997-57555P 19970829
AN 1999-214611 [18] WPIDS
AB WO 9911263 A UPAB: 20011203

NOVELTY - Use of a synergistic combination of amlodipin (I) and a statin (II) compound produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.

DETAILED DESCRIPTION - A composition comprises:
(a) (I) (disclosed in US 4,572,909) or a salt;
(b) (II) (not atorvastatin) or a salt; and
(c) a **carrier** or diluent.

INDEPENDENT CLAIMS are included for the following:
(i) separate compositions of (I) and (II) for use together
(ii) a kit comprising (a), (b), (c) in a container.

ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.

MECHANISM OF ACTION - Calcium channel blocker (I); HMG-CoA reductase inhibitor (II).

USE - The combination is useful for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.

ADVANTAGE - The combination of (a) and (b) is synergistic. No suitable data given.

Dwg.0/0

L6 ANSWER 19 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-204972 [17] WPIDS
DOC. NO. CPI: C1999-059655
TITLE: Use of a synergistic combination of atorvastatin and antihypertensive agent for treating angina pectoris and atherosclerosis.
DERWENT CLASS: B03 B05
INVENTOR(S): SCOTT, R A D
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC
COUNTRY COUNT: 84
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9911260 | A1 | 19990311 | (199917)* | EN | 51 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW | | | | | |
| W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW | | | | | |
| AU 9884589 | A | 19990322 | (199931) | | |
| ZA 9807839 | A | 20000426 | (200027) | | 49 |
| NO 2000000996 | A | 20000427 | (200032) | | |
| EP 1009400 | A1 | 20000621 | (200033) | EN | |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO SE SI | | | | | |
| CZ 2000000342 | A3 | 20000816 | (200048) | | |
| BR 9811556 | A | 20000822 | (200050) | | |
| CN 1268053 | A | 20000927 | (200067) | | |
| SK 2000000143 | A3 | 20001211 | (200103) | | |
| HU 2000004318 | A2 | 20010528 | (200140) | | |
| KR 2001022477 | A | 20010315 | (200159) | | |
| JP 2001514223 | W | 20010911 | (200167) | | 57 |
| AU 740424 | B | 20011101 | (200175) | | |
| AU 2002014783 | A | 20020321 | (200230)# | | |

APPLICATION DETAILS:

| PATENT NO | KIND | | APPLICATION | DATE |
|---|---|---|---|---|
| WO 9911260 | A1 | | WO 1998-IB1230 | 19980811 |
| AU 9884589 | A | | AU 1998-84589 | 19980811 |
| ZA 9807839 | A | | ZA 1998-7839 | 19980828 |
| NO 2000000996 | A | | WO 1998-IB1230 | 19980811 |
| | | | NO 2000-996 | 20000228 |
| EP 1009400 | A1 | | EP 1998-935250 | 19980811 |
| | | | WO 1998-IB1230 | 19980811 |
| CZ 2000000342 | A3 | | WO 1998-IB1230 | 19980811 |
| | | | CZ 2000-342 | 19980811 |
| BR 9811556 | A | | BR 1998-11556 | 19980811 |
| | | | WO 1998-IB1230 | 19980811 |
| CN 1268053 | A | | CN 1998-808463 | 19980811 |
| SK 2000000143 | A3 | | WO 1998-IB1230 | 19980811 |
| | | | SK 2000-143 | 19980811 |
| HU 2000004318 | A2 | | WO 1998-IB1230 | 19980811 |
| | | | HU 2000-4318 | 19980811 |
| KR 2001022477 | A | | KR 2000-701062 | 20000131 |
| JP 2001514223 | W | | WO 1998-IB1230 | 19980811 |
| | | | JP 2000-508363 | 19980811 |
| AU 740424 | B | | AU 1998-84589 | 19980811 |
| AU 2002014783 | A | Div ex | AU 1998-84589 | 19980811 |
| | | | AU 2002-14783 | 20020201 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9884589 | A | Based on | WO 9911260 |
| EP 1009400 | A1 | Based on | WO 9911260 |
| CZ 2000000342 | A3 | Based on | WO 9911260 |
| BR 9811556 | A | Based on | WO 9911260 |
| HU 2000004318 | A2 | Based on | WO 9911260 |
| JP 2001514223 | W | Based on | WO 9911260 |
| AU 740424 | B | Previous Publ. | AU 9884589 |
| | | Based on | WO 9911260 |
| AU 2002014783 | A | Div ex | AU 740424 |

PRIORITY APPLN. INFO: US 1997-57276P 19970829; AU 2002-14783 20020201

AN 1999-204972 [17] WPIDS

AB WO 9911260 A UPAB: 20011203

NOVELTY - Use of a combination of atorvastatin and an antihypertensive agent produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.

DETAILED DESCRIPTION - A composition comprises:

(a) atorvastatin (disclosed in US4681893) or a salt;

(b) an antihypertensive agent (not **amlodipine**) or a salt; and

(c) a **carrier** or diluent.

INDEPENDENT CLAIMS are included for separate compositions of (a) and (b) for use together, and kits containing combinations of (a) and (b).

ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.

MECHANISM OF ACTION - None given.

USE - The combination is useful for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.

ADVANTAGE - The combination of (a) and (b) is synergistic.

Dwg.0/0

L6 ANSWER 20 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1999-204971 [17] WPIDS
DOC. NO. CPI: C1999-059654
TITLE: Use of a synergistic combination of **amlodipine** and atorvastatin for treating angina pectoris and atherosclerosis.
DERWENT CLASS: B03
INVENTOR(S): BUCH, J; SCOTT, R A D
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC
COUNTRY COUNT: 84
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 9911259 | A1 | 19990311 | (199917)* | EN | 50 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW | | | | | |
| W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW | | | | | |
| AU 9885548 | A | 19990322 | (199931) | | |
| ZA 9807844 | A | 20000426 | (200027) | | 50 |
| NO 2000000998 | A | 20000228 | (200029) | | |
| EP 1003503 | A1 | 20000531 | (200031) | EN | |
| R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO SE SI | | | | | |
| CZ 2000000511 | A3 | 20000614 | (200037) | | |
| BR 9812030 | A | 20000926 | (200051) | | |
| CN 1268052 | A | 20000927 | (200067) | | |
| SK 2000000204 | A3 | 20001211 | (200103) | | |
| HU 2000003656 | A2 | 20010328 | (200124) | | |
| KR 2001023498 | A | 20010326 | (200161) | | |
| JP 2001514222 | W | 20010911 | (200167) | | 65 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 9911259 | A1 | WO 1998-IB1225 | 19980811 |
| AU 9885548 | A | AU 1998-85548 | 19980811 |
| ZA 9807844 | A | ZA 1998-7844 | 19980828 |
| NO 2000000998 | A | WO 1998-IB1225 | 19980811 |
| | | NO 2000-998 | 20000228 |
| EP 1003503 | A1 | EP 1998-936587 | 19980811 |
| | | WO 1998-IB1225 | 19980811 |
| CZ 2000000511 | A3 | WO 1998-IB1225 | 19980811 |
| | | CZ 2000-511 | 19980811 |
| BR 9812030 | A | BR 1998-12030 | 19980811 |
| | | WO 1998-IB1225 | 19980811 |
| CN 1268052 | A | CN 1998-808460 | 19980811 |
| SK 2000000204 | A3 | WO 1998-IB1225 | 19980811 |
| | | SK 2000-204 | 19980811 |
| HU 2000003656 | A2 | WO 1998-IB1225 | 19980811 |
| | | HU 2000-3656 | 19980811 |
| KR 2001023498 | A | KR 2000-702144 | 20000229 |
| JP 2001514222 | W | WO 1998-IB1225 | 19980811 |
| | | JP 2000-508362 | 19980811 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9885548 | A | Based on | WO 9911259 |
| EP 1003503 | A1 | Based on | WO 9911259 |
| CZ 2000000511 | A3 | Based on | WO 9911259 |
| BR 9812030 | A | Based on | WO 9911259 |
| HU 2000003656 | A2 | Based on | WO 9911259 |
| JP 2001514222 | W | Based on | WO 9911259 |

PRIORITY APPLN. INFO: US 1997-57275P 19970829
AN 1999-204971 [17] WPIDS
AB WO 9911259 A UPAB: 20011203
NOVELTY - Use of a combination of **amlodipine** and atorvastatin produces a synergistic antihypertensive, hypolipidemic, antianginal or antiatherosclerotic effect.
DETAILED DESCRIPTION - A composition comprises:
(a) **amlodipine** (I) (disclosed in US 4,572,909) or a salt;
(b) atorvastatin (II) (disclosed in US 4,681,893) or a salt; and
(c) a **carrier** or diluent.
INDEPENDENT CLAIMS are included for separate compositions of (I) and (II) for use together, and kits containing combinations of (I) and (II).
ACTIVITY - Antihypertensive; hypolipidemic; antianginal; antiatherosclerotic.
MECHANISM OF ACTION - None given.
USE - The combination is useful for treating angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and subjects with symptoms of cardiac risk.
ADVANTAGE - The combination of (I) and (II) is synergistic.
Dwg.0/0

L6 ANSWER 21 OF 22 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-051911 [06] WPIDS
DOC. NO. NON-CPI: N1996-043499
DOC. NO. CPI: C1996-017026
TITLE: Unit dose delivery system for hydrophobic drugs - comprises layers of hydrophilic material over hydrophobic material.
DERWENT CLASS: A96 B07 P33
INVENTOR(S): VERONESI, P A; VERONESI, P
PATENT ASSIGNEE(S): (THER-N) THERAPICON SRL
COUNTRY COUNT: 66
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| GB 2290965 | A | 19960117 | (199606)* | | 68 |
| WO 9601612 | A1 | 19960125 | (199610) | EN | 70 |
| RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ UG | | | | | |
| W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TT UA UG US UZ VN | | | | | |
| AU 9529252 | A | 19960209 | (199619) | | |
| ZA 9505741 | A | 19970326 | (199718) | | 71 |
| EP 769938 | A1 | 19970502 | (199722) | EN | |
| R: AT BE CH DE ES FR GB GR IE IT LI NL PT SE | | | | | |
| ES 2104522 | T1 | 19971016 | (199748) | | |
| JP 10502376 | W | 19980303 | (199819) | | 47 |

KR 97704427 A 19970906 (199839)
US 5814338 A 19980929 (199846)
EP 769938 B1 19981028 (199847) EN
R: AT BE CH DE ES FR GB GR IE IT LI NL PT SE
DE 69505671 E 19981203 (199903)
ES 2104522 T3 19990316 (199918)
AU 707076 B 19990701 (199937)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| GB 2290965 | A | GB 1994-13951 | 19940711 |
| WO 9601612 | A1 | WO 1995-EP2488 | 19950624 |
| AU 9529252 | A | AU 1995-29252 | 19950624 |
| ZA 9505741 | A | ZA 1995-5741 | 19950711 |
| EP 769938 | A1 | EP 1995-924940 | 19950624 |
| | | WO 1995-EP2488 | 19950624 |
| ES 2104522 | T1 | EP 1995-924940 | 19950624 |
| JP 10502376 | W | WO 1995-EP2488 | 19950624 |
| | | JP 1996-504081 | 19950624 |
| KR 97704427 | A | WO 1995-EP2488 | 19950624 |
| | | KR 1997-700142 | 19970110 |
| US 5814338 | A | WO 1995-EP2488 | 19950624 |
| | | US 1997-765952 | 19970109 |
| EP 769938 | B1 | EP 1995-924940 | 19950624 |
| | | WO 1995-EP2488 | 19950624 |
| DE 69505671 | E | DE 1995-605671 | 19950624 |
| | | EP 1995-924940 | 19950624 |
| | | WO 1995-EP2488 | 19950624 |
| ES 2104522 | T3 | EP 1995-924940 | 19950624 |
| AU 707076 | B | AU 1995-29252 | 19950624 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9529252 | A | Based on | WO 9601612 |
| EP 769938 | A1 | Based on | WO 9601612 |
| ES 2104522 | T1 | Based on | EP 769938 |
| JP 10502376 | W | Based on | WO 9601612 |
| KR 97704427 | A | Based on | WO 9601612 |
| US 5814338 | A | Based on | WO 9601612 |
| EP 769938 | B1 | Based on | WO 9601612 |
| DE 69505671 | E | Based on | EP 769938 |
| | | Based on | WO 9601612 |
| ES 2104522 | T3 | Based on | EP 769938 |
| AU 707076 | B | Previous Publ. | AU 9529252 |
| | | Based on | WO 9601612 |

PRIORITY APPLN. INFO: GB 1994-13951 19940711
AN 1996-051911 [06] WPIDS
AB GB 2290965 A UPAB: 19981028
Unit dosage delivery system (UDS) comprises (a) a capsule housing consisting of two or more couple layers, sheaths or films from different materials, the outer layer or sheath having a hydrophilic character and the inner sheath or films having a hydrophobic character; (b) a filling comprising one or more active hydrophobic drugs opt. with extended drug properties. Also claimed is a medicated compsn. comprising a **carrier** and a unit drug delivery system contg. (i) a capsule

housing comprising: (a1) an outer hydrophilic layer consisting of gelatin, glycerin and/or modified sorbitol soln., water or other suitable cpds. such as polyphenol cpds.; (b1) an inner hydrophobic silicone, silicone mixt. or silicone polymer layer; and (c1) opt. inner third or additional films or sheaths made from silicone polymers or waxes, or jaluronic acid polymers; and (ii) a capsule filling comprising: (a2) one or more drug substances admixed, dissolved, suspended or agglomerated in a hydrophobic support; (b2) silicone resin having a viscosity of 100-110 cSt and a specific gravity of 0.96-1.02; and (c2) opt. release modifying substances providing extended release of the drug selected from beeswax, silicone waxes and natural or modified stearic acid, palmitic acid, myristic acid, lauric acid, stearyl alcohol, cetyl alcohol, glycerol stearate, ethyl oleate, arachids oil, cottonseed oil, rapeseed oil, liq. paraffin or polyethylene glycol (400-200,000).

USE - The capsule contains drugs pref. oligopeptides, peptides, proteins, prostaglandins, cholesterol lowering agents, gastric antisecretories, antiacids, antiallergic agents, antiasthmatic agents, ACE inhibitors, antineoplastic agents, antiviral nucleoside agents, antiParkinson agents, antiepileptic agents, analgesics, non-steroidal antiinflammatories, antitussives, decongestionants, narcotics, antibiotics, cardiovasculars, their salts, lyophylised yeasts, vitamins or a vaccine, esp. the drug is cholera, typhoid or poliomyelitis vaccine, a calcitonin, erythropoietin, insulin, cyclosporin, lysozyme, typsin, carboxypeptidase, interleukin-1, prostaglandin A1, E2, F2 a or I2, misoprostol, thromboxane, eicosapentaenoic acid, docosahexanenoic acid, omeprazole, lansoprazole, rapitidine, sodium bicarbonate cetirezine, bamiphylline, captopril, enalapril, etoposide, sodium restramustine phosphate, acyclovir, selegiline, lamotrigine, aspirin, piroxicam, ketorolac, nifedipine, **amlodipine**, ditialzem, nicorandil, Lactobacillus bifidus or Lactobacillus bulgaricus.

ADVANTAGE - The UDS gives the drug protection against the atmosphere, oxidation, or moisture induced hydrolytic or degradation processes, allows a capsule filling moisture content <1%, minimises the diffusion of residue water from the external capsule housing to the filling, or of a water soluble active agent to the outer housing, causes unpleasant tastes or odours, controls or improves efficiently the site of action of the drug, prolongs when necessary, the release of the above agent from the filling, and avoids incompatibilities between the drug and auxiliary or optional ingredients. The UDS also allows delicate or unstable drugs to be formulated and delivered, enhances the protective conditions and prolongs the stability of the formulation.

Dwg.0/3

L6 ANSWER 22 OF 22 JAPIO COPYRIGHT 2002 JPO

ACCESSION NUMBER: 2000-044475 JAPIO

TITLE: SUPPRESSION OF MIGRATION OF SMOOTH MUSCLE CELL BY (R)-**AMLODIPINE**

INVENTOR: CHAHWALA SURESH BABUBHAI; WINSLOW DEREK PAUL

PATENT ASSIGNEE(S): PFIZER INC)

PATENT INFORMATION:

| PATENT NO | KIND | DATE | ERA | MAIN IPC |
|---|---|---|---|---|
| JP 2000044475A | | 20000215 | Heisei | A61K031-44 |

JP

APPLICATION INFORMATION

| | | |
|---|---|---|
| ST19N FORMAT: | JP1994-208778 | 19940810 |
| ORIGINAL: | JP11208778 | Heisei |
| PRIORITY APPLN. INFO.: | GB1993 9317773 | 19930826 |

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AB PROBLEM TO BE SOLVED: To obtain a composition capable of greatly suppressing the migration of smooth muscle cells in spite of practically showing no calcium channel blocking activity, and useful for the treatment of e.g. atherosclerosis by including an R(+) isomer of **amlodipine**, a **carrier** and so on.

SOLUTION: This composition is obtained by including (A) an R(+) isomer of **amlodipine** or a pharmacologically permissible salt thereof and (B) a pharmacologically permissible **carrier** or diluent. In the case of a preparation for oral administration, the component A is pref. included at 1-100 mg. In the case of a preparation for intravenous administration, the component A is pref. included at 1-20 mg. This composition is useful for the treatment e.g. of early recurrent stenosis post angioplasty and endometriosis.